8-5-2020

Menopause in Brazilian women with sickle cell anemia with and without hydroxyurea therapy.

Ana Mach Queiroz
Instituto de Hematologia Arthur de Siqueira Cavalcanti (HEMORIO)

Clarisse Lopes de Castro Lobo
Instituto de Hematologia Arthur de Siqueira Cavalcanti (HEMORIO)

Samir K. Ballas
Thomas Jefferson University; Instituto de Hematologia Arthur de Siqueira Cavalcanti (HEMORIO)

HEMATOL TRANSFUS CELL THER. 2020;xxx(xx):xxx–xxx

HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.htct.com.br

Letter to the Editor

Menopause in Brazilian women with sickle cell anemia with and without hydroxyurea therapy

Introduction

Women with sickle cell anemia (SCA) require special attention for myriad obstetric and gynecologic issues associated with this complex hematologic disorder. These affect all aspects of female life from menarche through menopause. Information regarding obstetric and gynecologic complications of sickle cell disease (SCD), with a few exceptions, is based primarily on observational, anecdotal, retrospective, or cohort studies that may not reflect current aspects of obstetric care.[1] Similarly, there are no recent reports about menopause (also known as climacteric) in women with SCA. The fact that life expectancy of women with SCA was determined to be 46–48 years[2] delayed studies about menopause. The recent improved survival of patients with SCA resulted in women reaching the age that is usually associated with the onset of menopause. The purpose of this letter is to determine if the onset of menopause is early or late in women with SCA and if hydroxyurea affects the onset of menopause.

Methods

Fifteen Brazilian women with sickle cell anemia (SCA) who were followed in the sickle cell program of the Department of Hematology, Instituto de Hematologia Arthur de Siqueira Cavalcanti (HEMORIO), Rio de Janeiro, RJ, Brazil were included in this study. Only women who had menopause for the previous two years were enrolled in the study. Menopause was defined by the cessation of menstruation for 12 consecutive months.[3] This was a questionnaire study. Personal interviews were conducted with each patient. Questions included age of menarche and menopause, intake of hydroxyurea (HU), frequency of painful episodes before and after menopause and the effect of menopause on hot flashes, insomnia, depression, anxiety, vaginal dryness and decreased libido.[4] Follicle-stimulating hormone (FSH) and estradiol were not measured. The dose of HU was 15 mg/kg/day by mouth for the patients taking it.

Mean and standard deviation were calculated via basic statistics in Systat 13. The continuous variables studied had symmetric distribution and analysis of the data used the paired t test to compare the variables mentioned. We also compared variables using the Friedman Test. Significance was based on a p value equal to 0.05 or less.

Laboratory data from medical records were also obtained retrospectively. All these parameters were identified two years before the onset of menopause and two years after its onset. The study was approved by the local institutional review board.

Results

Table 1 lists the age of the women enrolled in the study at menarche and menopause and whether they were on HU or not. The age of menarche in the general population is about 13 years and about 15 years in SCA.[1] Since HU was not available when the patients studied were in their teens, its effect on the age of menarche is not known to date. However, HU lowers the age of menopause significantly: (44.4 vs 49.3, $p = 0.03$).

The clinical observations by the women studied after the onset of menopause are also summarized in Table 1. The majority of the women (80%) indicated that the severity of sickle cell pain decreased after menopause. This salutary effect was counter-balanced by the signs and symptoms of menopause, most notably hot flashes, insomnia, depression and anxiety.

Supplementary Table 1 compare pertinent lab data before and after menopause in patients taking HU or not respectively and in all patients. The change in RBC indices and Hb F are obviously due to HU.

Discussion

Early obstetric reports stressed the decreased incidence of pregnancy in SCA, increased maternal and fetal death, recurrent miscarriages, and the impact of pregnancy on the clinical course of SCA. However, most of these reports were not confirmed by controlled trials.

Please cite this article in press as: Queiroz AM, et al. Menopause in Brazilian women with sickle cell anemia with and without hydroxyurea therapy. Hematol Transfus Cell Ther. 2020. https://doi.org/10.1016/j.htct.2020.06.009

Table 1 – Clinical data at menopause of Brazilians with sickle cell disease (SCD) taking or not taking hydroxyurea (HU).

	Age (years)[a]	VOCs/year	Decreased pain intensity	Hot flashes	Insomnia	Depression	Anxiety	Vaginal dryness	Decreased libido
Total number of patients (n = 15)	46.4 ± 4.87	Decreased	12	12	11	5	9	8	9
SCD/HU (n = 9)	44.4 ± 4.88	Decreased	7	6	8	3	7	5	4
SCD/No HU (n = 6)	49.3 ± 3.33	Decreased	5	6	3	2	2	3	5
Brazilians without SCD (n = 456)	51.2 ± 5.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

HU: hydroxyurea; n: number; N/A: not applicable; NS: not significant; VOCs: vaso-occlusive crises.

[a] Mean ± standard deviation calculated by basic statistics using Systat 13.

Women with SCA require special attention for the many obstetric and gynecologic issues associated with this complex disease. All aspects of female life from menarche through menopause are based primarily on observational, anecdotal, retrospective, or cohort studies that may not reflect current aspects of obstetric care.[1]

Growth and development of children with SCA are impaired. Manifestations of growth failure include delayed skeletal maturation, deficits in weight and height, delayed pubertal development, delayed menarche, and delayed first pregnancy. The mean age at menarche in healthy control subjects is significantly earlier than in SCA.[1] Because of this, we thought that menopause may be similarly delayed in women with SCA. We were surprised to find that the opposite is true.

Although puberty and menarche are delayed in patients with SCD, normal sexual maturation is attained by the majority of patients later in life, suggesting that these delays are due to constitutional rather than primary endocrinologic factors.[1]

Reports specifically addressing menopause in SCD are very few in the English literature.

One study mentions that 13 postmenopausal patients were among the patients enrolled in a bone mass density study, but no specific details about these patients were described. The study found no correlation between bone mass density and age, sex, or menopause.[5] A recent review indicated that premature menopause is a risk factor for infertility in women with SCD.[6]

Little is known about menopause in patients with SCA. The main reason is that the median life expectancy of women with SCA is about 48 years.[2] Because of this, both patients and providers did not worry about menopause in women with SCA. This is changing as the life expectancy of patients with SCD is increasing gradually.

We must emphasize that the number of patients described in this study is too small to make definitive conclusions. Nevertheless, it may suggest the presence of certain trends. Thus, menopause seems to be associated with decreased frequency of vaso-occlusive crises (VOCs) and decreased pain severity. This salutary effect, however, seems to be counterbalanced by the relative increase in insomnia, anxiety and depression.

Since the onset of menarche in patients with SCA is delayed as mentioned above,[1] one would expect that menopause may be delayed as well. This does not seem to be the case. The mean age of menopause in Brazilian women in the general population is 51.2 years.[7] This study shows the mean age of menopause of women with SCD is less than 51.2 years (Table 1). In addition, the mean age of menopause in women taking HU tends to be even lower than that of women not taking HU (44.4 vs 49.3, $p = 0.03$ using the t score test). This is consistent with the finding that HU decreases the Anti-Müllerian hormone (AMH) in women with SCA which, in turn, decreases the ovarian reserve associated with early menopause.[8,9]

The AMH is a serum marker of ovarian reserve[9] and is a predictor of the time of menopause.[10] Women with SCD have decreased levels of AMH[9] and HU decreases it further.[8] This study suggests HU is associated with menopause at an earlier age in SCA than in those not on HU.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgement

Supported in part by the Office of the Secretary of Health for the State of Rio de Janeiro and the Brazilian Ministry of Health.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.htct.2020.06.009.

REFERENCES

1. Ballas SK. Chapter 15: obstetrics, gynecology, and sickle cell pain. In: Sickle cell pain. 2nd edition Washington DC: International Association for the Study of Pain; 2014. p. 499–520.
2. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639–44.
3. Potter B, Schrager S, Dalby J, Torell E, Hampton A. Menopause. Prim Care. 2018;45(4):625–41.
4. Takahashi TA, Johnson KM. Menopause. Med Clin North Am. 2015;99(3):521–34.
5. Sarrai M, Duroseau H, D'Augustine J, Moktan S, Bellevue R. Bone mass density in adults with sickle cell disease. Br J Haematol. 2007;136(4):666–72.

6. Ghafuri DL, Stimpson SJ, Day ME, James A, DeBaun MR, Sharma D. Fertility challenges for women with sickle cell disease. Expert Rev Hematol. 2017;10(10):891–901.
7. Pedro AO, Pinto Neto AM, Paiva LH, Osis MJ, Hardy E. Age at natural menopause among Brazilian women: results from a population-based survey. Cad Saude Publica. 2003;19(1):17–25.
8. Elchuri SV, Williamson RS, Clark Brown R, et al. The effects of hydroxyurea and bone marrow transplant on Anti-Mullerian hormone (AMH) levels in females with sickle cell anemia. Blood Cells Mol Dis. 2015;55(1):56–61.
9. Kopeika J, Oyewo A, Punnialingam S, Reddy N, Khalaf Y, Howard J, et al. Ovarian reserve in women with sickle cell disease. PLoS One. 2019;14(2):e0213024.
10. Kruszynska A, Slowinska-Srzednicka J. Anti-Mullerian hormone (AMH) as a good predictor of time of menopause. Prz Menopauzalny. 2017;16(2):47–50.

Ana Mach Queiroz [a], Clarisse Lopes de Castro Lobo [a], Samir K. Ballas [a,b,*]

[a] *Instituto de Hematologia Arthur de Siqueira Cavalcanti (HEMORIO), Rio de Janeiro, RJ, Brazil*
[b] *Cardeza Foundation for Hematologic Research, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA*

[*] *Corresponding author at*: Cardeza Foundation for Hematologic Research, Department of Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, 1020 Locust St, Suite390, Philadelphia, PA19107, USA.
E-mail address: samir.ballas@jefferson.edu (S.K. Ballas).

Received 17 March 2020
2531-1379/

https://doi.org/10.1016/j.htct.2020.06.009
Available online xxx